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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEU, CHANGHWA J	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,406	ALEXANDER ET AL.	
	Examiner	Art Unit	
	JACOB CHEU	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-35* is/are pending in the application.

4a) Of the above claim(s) *29-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's amendment and filed on 2/12/2010 and Rule 131/132 affidavit (note, Applicant's own post-filing non-patent publication) filed on 10/22/2009 have been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

Claims 1-21 and 36 have been cancelled.

Claims 22-35 are pending.

Currently, claims 22-28 and 35 are under examination. Claims 29-35 are withdrawn from further consideration.

2. Figure 1 has been received and entered.

3. Description on SEQ ID No. 2 has been corrected.

4. The objections on claims 22, 23, 24, 26-28 and 35 are withdrawn because of amendments.

5. The rejections on claims 22-28 and 35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn due to the newly amendments. However, new ground of rejection is set forth in this Office Action with regard to clarity of the claim language (See below).

6. The rejections on claims 22-28 and 35-36 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement are **maintained** as of record (See discussion below).

7. The rejection on claim 36 under 35 U.S.C. 102(a) as being anticipated by Zimmermann et al. (Molecular Human Reproduction 2003 Vol. 9, page 81-89) is moot due to canceling of claim 36.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 22-28 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This is a **new ground of rejection** in view of the newly submitted amendments.

With respect to claim 22, line 7, it is not clear about the wording on SEQ ID No. 9, particularly β6 and β7. Are these two subnits? If this is the case, two sequence should be here. Please clarify.

With respect to claim 22, it is not clear what is function of measuring SEQ ID No. 9 in the claimed method. Please clarify.

Response to Applicant's Arguments on enablement issue

In affidavit, Applicant submitted a post-filing publication which has been six years later after the priority date (Biology of Reproduction 2009 Vol. 80, page 1053-1065; note the priority date for the instant application is 6/6/2003). The gist of the arguments lies on the results of this publication, herein abbreviated as Zimmermann et al. reference.

The Remarks states:

In the study underlying the document the concentration of βhCG and its proportion compared to total hCG in endometrial specimens was determined, *see* Zimmermann et al., Figure 2 and section "Evidence for the Presence-of hCG in Endometrial Tissue Homogenates and Intrauterine Secretion Material", spanning pages 1055 and 1056. The inventors have shown in said study that the proportion and the amount of βhCG in the endometrium is at highest levels during mid secretory and late secretory phase, respectively, whereas nearly undetectable during proliferative phase, see Zimmermann et al., Figure 2, and abstract, antepenultimate sentence: "Glandular endometrial hCG production is demonstrated immunoliistochemically, with an increase toward the late secretory phase vs. the early secretory phase of the normal secretory menstrual cycle."

Furthermore, the data presented in said document leads to the conclusion that the endometrial hCG is an important factor for the receptiveness of the endometrium and an undisturbed pregnancy, see Zimmermann et al., abstract, last sentence: "Endogenous endometrial hCG may be important for implantation and maintenance of pregnancy."

Even though it is formulated in the subjunctive, the conclusion is unambiguously derivable for a person of ordinary skill in the art from the data presented. Thus, Zimmermann *et al.* confirms the correlation between the concentration of endometrial βhCG and the receptiveness of the endometrium for fertilized eggs as disclosed in the present application. It follows that the method according to the invention is suited for the determination of the receptiveness of the endometrium for fertilized eggs.

Applicant's arguments have been considered, but are not persuasive.

Examiner acknowledges the clinical experiments conducted by the Applicants, albeit this came almost six years later after the conception of the idea. However, in view of Zimmermann et al. reference, Examiner could not agree with the conclusion of this reference is in commensurate with what is asserted in the claims.

The purpose of this paper is:

"The objective of this study was to determine whether beta human chorionic gonadotropin (hCG) (*CGB*) subunits and alpha hCG (*CGA*) subunits are expressed and

the hCG dimer is produced in ***normal*** human cyclic endometrium" (see the beginning of the Abstract)(emphasis added). Note, it is not clear whether the so-called CGB is the same as the eβhCG (SEQ ID No. 10). Please verify.

The Remarks points to Figure 2 for support " Glandular endometrial hCG production is demonstrated immunoliistochemically, with an increase toward the late secretory phase vs. the early secretory phase of the normal secretory menstrual cycle" (see Remarks, page 12). However, Figure 2 merely states:

"The total hCG hormone concentrations measured in homogenate supernatants increased from negligible values during the proliferative phase to higher values until the late secretory phase. There was a significant difference between the early secretory phase values and the late secretory phase values ($P < 0.010$). Free *CGB* subunit concentrations corresponded to about one tenth of the dimeric hCG concentration, as evidenced by the peripheral blood ratio. The LH concentrations tended to be at the low limit of detection and were negligible (Fig. 2)."

The results do not extend to whether such observation can be applicable to evaluate receptiveness for egg implantation or not, particularly when comparing with the recited criteria in claim 22. For instance, if the CGB is present in the non-pregnant women, does it really mean receptivness of a fertilized egg? Note, the CGB expresses marginally throughout the cycles (See Figure 2 (B)). Does only the late secretory phase account for this since the first three stages do not show any significant difference in the level of CGB.

Further, all the experimental data do not address the claimed invention. The next experiment is the "Expression of CGB and CGA mRNA in Endometrial Gland Epithelium". The results show " *CGB* expression began in the early secretory phase and increased to the midsecretory and late secretory phases relative to the amount of constitutive *GAPDH* expression (Fig. 5)".

Further, the subsequent experiment is "Production of Endometrial hCG molecule Forms Evidenced by Western Blotting". This simply " The molecular expression profiles correlate with known molecular isoforms of placental hCG such as those found in serum during pregnancy."

Later "Immunohistochemical Demonstration of hCG Secretion in the **Normal** Secretory-Transformed Endometrial Epithelium" was conducted. Again, this is normal tissue.

Finally, immunohistochemistry coupled with tissue scoring were embarked to determine the secretory transformation of the endometrium (See Figure 8).

In Discussion, Zimmermann et al. indicate " The objective of our study was to prove that ***normal*** secretory endometrium is capable of producing both transcription and translation hCG subunits during the healthy menstrual cycle. The results herein demonstrate that the endometrium of women primarily during the secretory phase expresses, produces, and secretes dimeric hCG hormone in glandular and luminal epithelium. This endometrial hCG is characterized by *CGB* and *CGA* subunit sequence expression." (emphasis added).

Further, Zimmermann et al. states "As evidenced by immunohistochemical staining results, our findings suggest that endometrial hCG **may** contribute, as early as the early secretory phase, to glandular development, along with increased endometrial

vascularization, stromal differentiation, and proliferation or infiltration of endometrial mononuclear cells. Adequate glandular hCG secretion potentially optimizes secretory differentiation of fertile cyclic endometrium and prepares the tissue for embryo implantation and successful gestation." (emphasis added).

Although several physiological roles, such as " early secretory phase, to glandular development, along with increased endometrial vascularization, stromal differentiation, and proliferation or infiltration of endometrial mononuclear cells" may link to hCG, nevertheless thus far this is a speculation without evidential proof.

Further, Zimmermann et al. reinforce this view by saying "Because hCG expression correlates with progesterone stimulus, we **hypothesized** that hCG formation is a progesterone-induced process. Furthermore, because hCG is regarded as an immunoregulatory hormone, it **could have** an important role during implantation. Therefore, we **speculated** that endometrial hCG **may be** an **appropriate marker** to assess the receptivity of the endometrium for embryo implantation"(emphasis added).

Interesting, at page 1063, Zimmermann et al. states " We confirm much **higher** dimeric hCG concentrations compared with free *CGB* subunit concentrations in our results showing hCG release into the homogenate supernatant of high secretory cycle phase endometrium specimens, as well as in our **premenstrual peripheral blood measurements of hCG in patient studies** (data not shown)." It is not clear what kind of patients Zimmermann et al. refer to. The claim merely recites "wherein expression of eβhCG in samples derived from pregnant women signals an undisturbed pregnancy". The claimed invention merely needs to find the presence of the eβhCG. It is not clear

whether the data from Figure 2 of Zimmermann et al. were collected from patients alone, no non-pregnant women.

Finally, Zimmermann et al. in fact look forward for further verification of their speculation "In conclusion, this study demonstrates for the first time (to our knowledge) that *CGB* and *CGA* subunits and hCG are expressed and produced in glandular epithelium of synchronous progesterone-stimulated secretory endometrium. Maximal hCG production correlated with maximal mononuclear cell occurrence and with considerable vascularization. Therefore, we believe that endometrial hCG is a marker for receptivity of embryo implantation, **although further investigation is required**" (emphasis added).

Taken together, after six more years of exploring, Applicant has not shown sufficient evidence in support of the claimed invention. Thus, the enablement rejection is maintained.

Conclusion

10. No claim is allowed.
11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JACOB CHEU whose telephone number is (571)272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jacob Cheu/
Primary Examiner, Art Unit 1641